REMARKS

Claims 1, 2, 6-11, 13, 17, and 28-32 are currently pending in this application.

Applicant has amended claims 1, 2, 6-11, 13, 17, 28 and 30.

Applicant has amended claim 1 to more specifically describe the claimed method. Specifically, the method utilizes a compound capable of (1) ADP-ribosylating rho or rac or (2) physically interacting with rho or rac or an associated kinase and inhibiting complex formation or (3) inhibiting the kinase activity of a complex between either rho or rac and an associated kinase. Support for this amendment can be found, for example, in the specification on page 4, lines 7-9 (wherein it is stated that ADP-ribosylation of rho specifically inhibits the protein). Additional support may be found in the specification, for example, page 10, lines 10-17. The method of inhibiting rho or rac (resulting in CNS axon growth) is, thus, specifically recited as a method utilizing compounds that ribosylate rho or rac (thus rendering it incapable of binding to an effector kinase, i.e. ROCK), physically block complex formation between rho or rac and their associated kinase or physically interact with the complex of the associated kinase and activated rho or rac in such a manner that the kinase activity of the complex is inhibited.

Applicant has amended claim 2, 6, 7, 8, 13, 17, 28 and 30 to recite terms consistent with the above described amendment to claim 1. Claims 2, 6-11, 13, 17 and 29-30, which are each dependent claims, have been amended to begin with "the" instead of "a". In addition, various spelling corrections and claim dependencies have been corrected.

Applicant has added claim 31. Support for claim 31 can be found in the specification as filed, for example, on page 10, lines 10-17. Applicant has amended claim 32. Support for claim 32 can be found in the specification as filed, for example, on page 10, lines 10-17.

None of the amendments presented herein constitute new matter. Applicant addresses below the outstanding rejections.

PRIORITY

Applicant has noted the Examiner's contention with respect to the priority dates of the pending claims. Applicant reserves the right to dispute these contentions.

THE OBJECTIONS

The Examiner has objected to claim 17 contending that the claim contained misspellings. Applicant has corrected the spelling of the words identified by the Examiner, thereby obviating this objection. The Examiner has objected to claim 23 as being duplicative of claim 7. Applicant has canceled claim 23, thereby obviating this objection. The Examiner has objected to claim 29, contending that it is duplicative of claim 28 and claim 13, contending that it is duplicative of claim 24. Applicant has amended claims 13 and 28, thus obviating this objection.

THE REJECTIONS

35 U.S.C. § 112, first paragraph

Claims 12 stands rejected under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner contends that the support was not cited for the claim when it was amended in April 23, 2001 response. Support for claim 12 can be found, for example, in the specification on page 10, lines 13-15. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

Claims 1-2, 6-13, 17, and 24-27 stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner contends that, while the claims are enabled for *in vitro* stimulation with C. botulinum C3 exoenzyme, the specification "does not reasonably provide enablement for in vivo promotion of CNS axon growth with generically recite rho protein inhibitors as claimed." Applicant traverses based on the amendments and arguments presented herein.

As an initial matter, applicant has amended the claims to recite a specific class of inhibitory compounds. In that respect, the claims can no longer be held to "generically recite rho protein inhibitors." Regarding the enablement or "correlation" of methods of treatment claims supported by in vitro models, MPEP 2164.02 states that

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays

> and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):
>
> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

In the June 17, 2003 Office Action, the Examiner contends that the system used by applicant is not predictive of *in vivo* success. However, as reiterated herein with respect to the outstanding § 103 rejection, applicant tested axon outgrowth on CNS myelin (which is inhibitory for axon outgrowth) and saw stimulation of axon extension. By testing on CNS myelin, applicant's assay is predictive for regeneration after injuries because the surface mimics that confronted by axons in the adult mammalian CNS. Applicant was the first to provide such evidence which clearly "correlates" to the in vivo setting. This model system at the very least provides a "reasonable correlation" to the amended method claims which recite a specific class of inhibitory molecules. Accordingly, applicant believes that the claims are enabled by the

compelling *in vitro* data presented in the application and respectfully requests that the Examiner reconsider and withdraw this rejection.

35 U.S.C. § 112, second paragraph

Claims 1-2, 6-13, 17, and 24-27 stand rejected under 35 U.S.C. § 112, second paragraph. Specifically, the Examiner contends that the claims do not provide "a definite means for assessing whether or not a compound should or should not be considered a rho inhibitor." Applicant traverses based on the amendments and arguments presented herein.

Applicant has amended the claims to specifically recite that the method utilizes inhibitors that either (1) ADP-ribosylate rho or rac, (2) block the interaction between an associated kinase and either rho or rac; or (3) physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and inhibit the kinase activity of the complex. Accordingly, the class of inhibitors would be definite to one of skill in the art. Applicant respectfully requests that the Examiner withdraw this rejection.

Claim 12 stands rejected under 35 U.S.C. § 112, second paragraph. Specifically, the Examiner contends that there is no antecedent basis for the referenced clause. Applicant canceled claim 12, thus obviating the rejection.

Claim 29 stands rejected under 35 U.S.C. § 112, second paragraph. Specifically, the Examiner contends that the claim lacks antecedent basis. Further, the Examiner contends that the claim is a substantial duplicate of claim 28. Applicant has amended claim 28 to recite the term referenced in claim 29 and to remove the redundancy with claim 29.

Claim 30 stands rejected under 35 U.S.C. § 112, second paragraph. Specifically, the Examiner contends that there is no antecedent basis for the term "the composition" and that it improperly depends from claim 28. Applicant has amended claim 28 and claim 30 to properly recite antecedent basis and to correct the dependency.

35 U.S.C. § 102 or 103

Claims 1, 2, 6, 12, 21-22 and 25-27 stand rejected under 35 U.S.C. § 102(b) as being "anticipated by" Bartsch or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over Bartsch. Applicants traverse based on the amendments and arguments presented herein.

The Examiner contends that Bartsch teaches the use of the IN1 antibody directed against neurite growth inhibitors NI-35 and NI250. However, applicant has amended the claims to specifically recite a method using inhibitors that (1) ADP-ribosylate rho or rac, (2) block the interaction between the associated kinase and either rho or rac; or (3) physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and inhibit the kinase activity of the complex. Because the IN1 antibody does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac, and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase, this amendment obviates the outstanding rejection.

Claims 1, 2, 6, 12, 21-22 and 25-27 stand rejected under 35 U.S.C. § 102(b) as being "anticipated by" Sylvain. Applicants traverse based on the amendments and arguments presented herein.

The Examiner contends that Sylvain teaches the use of Lovastatin in rho inhibition. However, applicant has amended the claims to specifically recite a method using inhibitors that (1) ADP-ribosylate rho or rac, (2) block the interaction between the associated kinase and either rho or rac; or (3) physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and inhibit the kinase activity of the complex. Because Lovastatin does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac, and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase, this amendment obviates the outstanding rejection.

Claims 1, 2, 6, 9, 11-12, 21-22 and 25-27 stand rejected under 35 U.S.C. § 102(b) as being "anticipated by" Varon as evidenced by Takashi. Applicant traverses based on the amendments and arguments presented herein.

The Examiner contends that Varon teaches the use of NGF in rho inhibition. However,

applicant has amended the claims to specifically recite a method using inhibitors that (1) ADP-ribosylate rho or rac, (2) block the interaction between the associated kinase and either rho or rac; or (3) physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and inhibit the kinase activity of the complex. Because NGF does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac, and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase, this amendment obviates the outstanding rejection.

Claims 1, 2, 6-7, 12-13, and 21-29 stand rejected under 35 U.S.C. § 102(e) as being "anticipated by" Johnson. Applicants traverse based on the amendments and arguments presented herein.

The Examiner contends that Johnson teaches the use of compounds capable of regulating $G_{\alpha}12$ and/or $G_{\alpha}13$ which, in turn, result in downstream rho inhibition. However, applicant has amended the claims to specifically recite a method using inhibitors that (1) ADP-ribosylate rho or rac, (2) block the interaction between the associated kinase and either rho or rac; or (3) physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and inhibit the kinase activity of the complex. Because $G_{\alpha}12$ and/or $G_{\alpha}13$ do not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac, and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase, this amendment obviates the outstanding rejection.

Claims 1, 2, 6, 10, 12, 21-22 and 25-27 stand rejected under 35 U.S.C. § 103(a) as being "obvious over" Mattson, Olson I, Olson II, and Varon as evidenced by Takashi. Applicants traverse based on the amendments and arguments presented herein.

The Examiner contends that Mattson, Olson I, Olson II, and Varon as evidenced by Takashi teaches the use of NGF in CNS regeneration. However, applicant has amended the claims to specifically recite a method using inhibitors that (1) ADP-ribosylate rho or rac, (2) block the interaction between the associated kinase and either rho or rac; or (3) physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and inhibit the kinase activity of the complex. Because NGF does not ADP-ribosylate rho

or rac, does not block the interaction between the associated kinase and either rho or rac, and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase, this amendment obviates the outstanding rejection.

Claims 1, 2, 6-13, 17, and 21-30 stand rejected under 35 U.S.C. § 103(a) as being "unpatentable over" Kamata, Varon, Mobley, Olson I, Olson II and Barth. Applicant traverses based on the amendments and arguments presented herein.

The Examiner contends that Kamata teaches chick dorsal root ganglia (DRG) induced nerve outgrowth via administration of C. botulinum C3 exoenzyme (ADP-ribosyltransferase) that is at least as effective as DRG outgrowth induced via NGF. Varon, Mobley, Olson I, and Olson II are cited for supposedly teaching the utillity of NGF. Barth is cited as supposedly teaching a C2/C3 fusion protein. Applicant traverses based on the amendments and arguments presented herein.

With respect to Kamata, this reference describes outgrowth on a surface that allows quite good growth. The authors observed some altered morphology with augmented neurite formation. Importantly, applicant tested outgrowth on CNS myelin (which is inhibitory for axon outgrowth) and saw stimulation of axon extension. By testing on CNS myelin, applicant's assay is predictive for regeneration after injuries because the surface mimics that confronted by axons in the adult mammalian CNS. Thus, not only is applicant's disclosure not obvious in light of Kamata, applicant's disclosure is more predictive of *in vivo* efficacy.

Secondly, it appears that Kamata's primary assays on neuroblastoma cells involved "differentiation" of neuroblastoma cells. In the basal state, these cells are tumor cells and are not neuron-like. However, they can be induced to change into neuron-like cells by many agents, including C3 in this study. It should be noted that these changes can be induced by many non-specific things, like serum withdrawal, in many neuroblastoma cells. This is nothing like increasing the axon growth rate from a full-fledged neuron, as in applicant's studies. Therefore, any outgrowth from chick ganglion would have been assumed more likely to relate to survival or differentiation or non-neuronal effects as opposed to indicating direct action on axon growth.

In conclusion, Kamata does not demonstrate increased axon outgrowth from differentiated neurons, and it clearly does not consider surfaces that mimic the environment encountered in vivo after damage to the CNS.

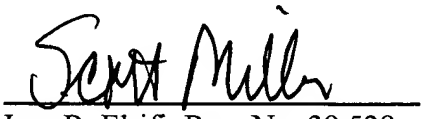
With respect to Varon, Mobley, Olson I, Olson II and Barth, applicant has amended the claims to specifically recite a method using inhibitors that (1) ADP-ribosylate rho or rac, (2) block the interaction between the associated kinase and either rho or rac; or (3) physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and inhibit the kinase activity of the complex. Because NGF does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac, and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase, this amendment obviates the outstanding rejection.

CONCLUSION

Applicant respectfully requests that the Examiner enter the requested amendment, reconsider and withdraw the outstanding rejections, and allow the pending claims to pass to issue.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 935-3000. All correspondence should continue to be directed to our address given below.

Respectfully submitted,



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